# Inhibition is associated with whole-brain structural brain connectivity on network level in school-aged children born very preterm and at term

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Abstract: Inhibition abilities are often impaired in children born very preterm. In typically-developing individuals, inhibition has been associated with structural brain connectivity (SC). As SC is frequently altered following preterm birth, this study investigated whether aberrant SC underlies inhibition deficits in school-aged children born very preterm. In a group of 67 very preterm participants aged 8–13 years and 69 term-born peers, inhibition abilities were assessed with two tasks. In a subgroup of 50 very preterm and 62 term-born participants, diffusion tensor imaging (DTI) data were collected. Using network-based statistics (NBS), mean fractional anisotropy (FAmean) was compared between groups. Associations of FAmean and inhibition abilities were explored through linear regression. The composite score of inhibition abilities was lower in the very preterm group (M = −0.4, SD = 0.8) than in the term-born group (M = 0.0, SD = 0.8) but group differences were not significant when adjusting for age, sex and socio-economic status ( = −0.13, 95%-CI [-0.30, 0.04], p = 0.13). In the very preterm group, FAmean was significantly lower in a network comprising thalamo-frontal, thalamo-temporal, frontal, cerebellar and intra-hemispheric connections than in the term-born group (t = 5.21, lowest p-value = 0.001). Irrespective of birth status, a network comprising parietal, cerebellar and subcortical connections was positively associated with inhibition abilities (t = 4.23, lowest p-value = 0.02). Very preterm birth results in long-term alterations of SC at network-level. As networks underlying inhibition abilities do not overlap with those differing between the groups, FAmean may not be adequate to explain inhibition problems in very preterm children. Future studies should combine complementary measures of brain connectivity to address neural correlates of inhibition abilities.

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# Inhibition is associated with whole-brain structural brain connectivity on network level in school-aged children born very preterm and at term

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A B S T R A C T

Inhibition abilities are often impaired in children born very preterm. In typically-developing individuals, inhibition has been associated with structural brain connectivity (SC). As SC is frequently altered following preterm birth, this study investigated whether aberrant SC underlies inhibition deficits in school-aged children born very preterm. In a group of 67 very preterm participants aged 8–13 years and 69 term-born peers, inhibition abilities were assessed with two tasks. In a subgroup of 50 very preterm and 62 term-born participants, diffusion tensor imaging (DTI) data were collected. Using network-based statistics (NBS), mean fractional anisotropy ($FA_{mean}$) was compared between groups. Associations of $FA_{mean}$ and inhibition abilities were explored through linear regression. The composite score of inhibition abilities was lower in the very preterm group ($M = -0.4$, $SD = 0.8$) than in the term-born group ($M = 0.0$, $SD = 0.8$) but group differences were not significant when adjusting for age, sex and socio-economic status ($\beta = -0.13$, 95%-CI [-0.30, 0.04], $p = 0.13$). In the very preterm group, $FA_{mean}$ was significantly lower in a network comprising thalamo-frontal, thalamo-temporal, frontal, cerebellar and intra-hemispheric connections than in the term-born group ($t = 5.21$, lowest $p$-value $= 0.001$). Irrespective of birth status, a network comprising parietal, cerebellar and subcortical connections was positively associated with inhibition abilities ($t = 4.23$, lowest $p$-value $= 0.02$). Very preterm birth results in long-term alterations of SC at network-level. As networks underlying inhibition abilities do not overlap with those differing between the groups, $FA_{mean}$ may not be adequate to explain inhibition problems in very preterm children. Future studies should combine complementary measures of brain connectivity to address neural correlates of inhibition abilities.

## 1. Introduction

Adverse effects of very preterm birth (i.e., <32 weeks of gestational age) have been reported on multiple behavioral, academic and cognitive domains (Allotey et al., 2018; Twilhaar et al., 2018). Among the abilities most frequently impaired are executive functions, a set of higher-order cognitive skills, which facilitate various aspects of goal-directed behavior (van Houdt et al., 2019; Diamond, 2013). Special research interest lies in inhibition abilities, since they are reported to form an elemental component of executive functioning and play a crucial part in the development of other executive functions (Miyake et al., 2000; Anderson, 2002; Aron et al., 2004; Best and Miller, 2010; Brocki and Bohlin, 2004). Inhibition abilities have been shown to be strong predictors of emotional regulation (Jahromi and Stifter, 2008), (social) behavior (Luna and Sweeney, 2004) and long-term academic success (Borst et al., 2014; Jaekel et al., 2016). There are ambiguous findings on inhibition abilities in individuals born very preterm, with evidence for inhibition deficits (Baron et al., 2012; Böhm et al., 2002; Böhm et al., 2004; Harvey et al., 1999; Loe et al., 2015; Pizzo et al., 2010; Brumbaugh et al., 2014; Witt et al., 2014; Aarnoudse-Moens et al., 2009a; Marlow et al., 2007; Orchinik et al., 2011; Cserjesi et al., 2012; Loe et al., 2012; Aarnoudse-Moens et al., 2012; de Kieviet et al., 2014; Ritter et al., 2013a;

*Abbreviations:* DTI, diffusion tensor imaging; FA, fractional anisotropy; SES, socioeconomic status; NBS, network-based statistics; ADHD, attention-deficit/hyperactivity disorder; Epo, erythropoietin; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SSRT, stop signal reaction time; MRI, magnetic resonance imaging; IQ, intelligence quotient; M, mean; SD, standard deviation; ODF, orientation density function; PDF, probability density function; ROI, region of interest; FOV, field of view; MD, mean diffusivity.

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Bayless and Stevenson, 2007; Mulder et al., 2011a; Ford et al., 2011; Luu et al., 2011), unimpaired inhibition abilities (Baron et al., 2012; Böhm et al., 2004; Brumbaugh et al., 2014; Aarnoudse-Moens et al., 2009a; Hodel et al., 2016; Potharst et al., 2013; Ni et al., 2011; Wolfe et al., 2015; de Kieviet et al., 2012), and a potential catch-up to term-born peers' abilities around middle school-age (Loe et al., 2012; Aarnoudse-Moens et al., 2012; de Kieviet et al., 2014; Ritter et al., 2013a; Elgen et al., 2004; Johnson et al., 2015; Réveillon et al., 2016; Anderson et al., 2011; Ritter et al., 2014; Shum et al., 2008; Kulseng et al., 2006; Nosarti et al., 2006) (for a comprehensive review see Réveillon et al., 2018).

Structural brain connectivity describes the presence, strength and integrity of white matter tracts connecting different brain regions and can be quantified in multiple measures of diffusion tensor imaging (DTI), such as mean fractional anisotropy ($FA_{mean}$) of water diffusion as a common measure of connection efficiency (Griffa et al., 2013). In typically developing children and adolescents, evidence has been reported that better inhibition abilities are associated with better structural brain connectivity in frontal, parietal and motor cortex regions as well as subcortical brain regions (Madsen et al., 2010; Seghete et al., 2013; Chaddock-Heyman et al., 2013). Further, based on measures of functional brain connectivity, meta-analytic evidence of a large-scale distributed brain network underlying inhibition abilities has been presented (Zhang et al., 2017). Together, this suggests that imaging approaches that regard the whole network topology should be best suited to determine the neural correlates of inhibition abilities in preterm-born compared to term-born children. So far, only a limited number of studies exist investigating the effects of preterm birth on the integrity of the whole-brain structural topology on network level in infancy (Batalle et al., 2017; Pandit et al., 2013; Ball et al., 2014; Tymofiyeva et al., 2012), at early school-age (Kim et al., 2014; Fischi-Gómez et al., 2014) and in adulthood (Karolis et al., 2016). To our knowledge, no study to date has investigated whole-brain structural connectivity on network level in children at middle school age. The current study, thus, aimed to 1) compare inhibition abilities between children born very preterm and at term at middle school age, 2) compare whole-brain structural connectivity on network level between groups, and 3) investigate potential associations between inhibition abilities and whole-brain structural connectivity on network level.

## 2. Materials and methods

### 2.1. Participants

The recruitment procedure of the EpoKids study, an ongoing prospective follow-up study investigating the long-term neuroprotective effect of erythropoetin (Epo) on executive functions in children born very preterm, has been reported previously (Wehrle et al., 2018). In short, very preterm infants (gestational age <32 weeks) born between 2005 and 2012 who participated in the randomized control trial "Does erythropoietin (Epo) improve outcome in preterm infants" (NCT00413946) and were followed-up at age two years (Natalucci et al., 2016) are eligible for the EpoKids study. The current analysis reports on children born between 2005 and 2009. Term-born children were recruited as friends and siblings of participants born very preterm, or via flyers, notices, and social media, and included into a control group. Inclusion criteria were birth at term (i.e., ≥37 weeks; 0 days of gestation), no neonatal complications and no neurodevelopmental or neurologic disease at present or in the past (i.e., ADHD, autism spectrum disorder, epilepsy, encephalopathy), as reported by the parents.

### 2.2. Study procedure

Assessments took place at the Child Development Center at the University Children's Hospital Zurich (exception: seven assessments in Geneva. For a detailed description, see *Results*) between July 2017 and September 2019, either on weekdays or weekends, at the families' convenience. In the course of one assessment day (approximately 7 hours), participants underwent a comprehensive neuropsychological test battery in a pseudo-randomized order. At the end of the assessment day, cerebral MRI took place at the MR center of the University Children's Hospital Zurich. The study was approved by the ethical committee of the Canton of Zurich. Parents of the study participants signed a written informed consent form. All participating children were asked for their verbal consent. They were compensated with a gift voucher.

### 2.3. Instruments and measures

For participants born very preterm, perinatal data were collected from the original randomized trial, conducted at the Department of Neonatology at the University Hospital Zurich. Socio-economic status (SES) was estimated using a six-point scale (1–6) based on maternal and paternal education (Largo et al., 1989). SES scores of both parents were summed, resulting in total SES scores ranging from 2 to 12. Higher values reflect higher SES. IQ was estimated with a 4-subtest combination of the Wechsler Intelligence Scale for Children (Petermann and Petermann, 2008): block design, similarities, digit span forward/backward, and coding (Waldmann, 2008).

### 2.4. Inhibition abilities

Two standardized neuropsychological tasks were administered in random order to investigate two key functions of inhibition abilities: 1) The stop signal paradigm is a computerized instrument assessing response inhibition. The participant is instructed to respond as quickly and correctly as possible to a go-stimulus (cartoon airplane) and to inhibit this action if a stop-stimulus (red frame around airplane) appears after presentation of the go-stimulus (25% of the trials). The delay of the stop-stimulus depends on the participant's performance: starting at 250 ms, it is increased by 50 ms if the participant inhibits a response correctly, and decreased by 50 ms if the child fails to inhibit a response. The task-related settings were resumed from a previous study with very preterm born children at school age (Aarnoudse-Moens et al., 2012). The outcome measure was the stop signal reaction time (SSRT), defined as the mean reaction time of the participant minus the mean delay of the stop-stimulus (Verbruggen and Logan, 2008). 2) The participants' interference control was assessed with the D-KEFS' Color-Word Interference Test (Delis et al., 2001). In this task, the participant is asked to name the ink colors of words that are presented in an incongruent ink color ('Stroop effect' (MacLeod, 1991)). As it has been reported previously that interference control is mediated by processing speed in children born very preterm (Mulder et al., 2011a), completion time for this task was adjusted for individual processing speed as assessed by naming colored fields as fast as possible. To allow for equally scaled results of both inhibition tasks, the completion times (in seconds) were *z*-transformed using the mean and standard deviation of the term-born group. The *z*-scores were subsequently averaged and combined into a composite score serving as an overall estimate of the participants' inhibition abilities (see Fig. S1 for information on the association between the individual tasks). Higher *z*-scores reflect better inhibition abilities.

### 2.5. Magnetic resonance imaging

Cerebral MRI was performed on a 3T GE MR750 scanner, using an 8-channel receive-only head coil. Hearing protection was provided to all participants with earplugs and headsets. The heart and respiratory rate was monitored continuously.

In the context of a comprehensive MRI study protocol including volumetric, structural, functional, and spectroscopy sequences, T1-weighted MR images with a 3D fast spoiled gradient echo sequence (echo time = 5 ms, repetition time = 11 ms, inversion time = 600 ms, flip angle = 8°, field of view (FOV) = 25.6 cm, reconstruction matrix: 256 × 256), and T2-weighted images with a fast recovery fast spin echo

sequence (echo time = 98 ms, repetition time = 2800 ms, FOV = 256 cm, matrix: 256 × 256) were acquired. DTI was performed using a pulsed gradient spin echo echo-planar imaging sequence with echo time = 77 ms, repetition time = 6500 ms, field of view = 27.8 cm, matrix = 96 × 96, slice thickness = 3.6 mm. The diffusion encoding scheme included 35 non-collinear gradient encoding directions with b = 1000 and four interleaved b = 0 images.

### 2.6. Diffusion tensor image processing

DTI data were visually assessed for artifacts by observing each diffusion gradient volume and each image slice for signal dephasing or spin history artifacts caused by movements. If the participant moved excessively during the DTI scan or the images showed grave artifacts induced by (partly) metallic dental braces, data were discarded and the participant was excluded. Participants were also excluded if more than three diffusion-weighting gradient volumes were corrupted by motion artifacts. Image frames and the corresponding entries in the b-matrix and b-value descriptor files were removed from further analysis if head movement caused extensive signal dropout throughout the brain in the given frame. The unprocessed DTI images were used to estimate an outline that separates the brain from non-neuronal tissues (brain masking) using the BET tool in the FSL software package (Smith, 2002). Each participant's brain mask was visually assessed, and upon inconsistency, manual corrections were performed. A custom script written in bash programming language for Linux was used to process the DTI images by wrapping previously published algorithms as described below. Spurious image shifts originating from eddy currents and real movement were corrected with the *eddy* command in the FSL software library (version 6.0). The CUDA 8.0 implementation was used for DTI correction, which included the slice-to-volume movement correction and outlier replacement. During this step, the following parameters were used: 2 standard deviations as criterion for classifying a slice as outlier (ol_nstd = 2), replacement of both positive and negative outliers (ol_pos), 6 slice to volume iterations (s2v_niter = 6), filter width to use for pre-filtering of data for the estimation process 10,6,4,2,0,0 mm for each subsequent iterations. Next, FA and mean diffusivity (MD) maps were calculated by running the *dtifit* command in FSL on the motion corrected DTI dataset.

### 2.7. Structural connectivity network construction

While DTI processing and tractography were performed in the native space of the DTI data, to obtain regions of interest (ROIs), the FMRIB58 FA template (MNI152 space) was transformed to the participants' FA image. A linear affine transformation (FLIRT, FSL) followed by a non-linear deformation (NIFTIreg software, *reg_f3d* command, control grid size: 5 * 5 * 5 mm, weight of the bending energy penalty term: 0.005, gradient smoothing with a kernel of 4 mm) was performed. This transformation was used to align the ROI system of the AAL atlas to the participants' DTI coordinate system.

Seed points for probabilistic diffusion tractography (probabilistic index of connectivity method as implemented in the Camino Diffusion Toolkit (Parker et al., 2003)) were defined as the voxels with FA $\geq$ 0.1 within a whole-brain mask. Orientation density functions (ODFs) were estimated using fourth order Spherical Harmonics and a maximum of two local ODF maxima were set to be detected at each voxel and probability density function (PDF) profile was produced from the local ODF maxima. Fiber tracking was carried out on the voxel-wise PDF profile with the Euler interpolation method using 10 iterations per each seed point. Tracing stopped at any voxel whose FA was less than 0.2.

Weighted, undirected structural connectivity networks were formed based on whole-brain probabilistic tractography by means of mean fractional anisotropy ($FA_{mean}$). Nodes corresponded to the AAL ROIs in participant space. In the $FA_{mean}$ structural connectivity network, the strength of each edge was given by the $FA_{mean}$ value of all tractography streamlines connecting the regions at the two end-points. To avoid systematic differences in absolute number of edges, we used a thresholding procedure based on network costs, which ensures similar network topology across participants by keeping the same number of strongest connections.

Network cost for each participant without thresholding (actual network edges/all possible edges) was calculated. We made three considerations when thresholding the connectivity matrices: first, our study is in part a case-control study where variable thresholding can introduce systematic differences between the very preterm and control groups. Secondly, we aim to reveal correlations irrespective of birth status, in which case between-group differences can be controlled for by including a grouping variable and the mean connectivity as covariates in the statistical models. Using an absolute threshold can lead to different numbers of network edges across datasets, and different levels of network density between control and patient cases (van Wijk et al., 2010). Third, to tackle false positive connections in the structural connectivity matrix. In proportional thresholding (van den Heuvel et al., 2017) potential between-group differences assumed to result from differences in the topological organization of edges and not due to differences in number of edges. We utilized a dual strategy: first to check whether overall structural connectivity differences exist between groups, and then carry out proportional thresholding to select the threshold where very preterm and control differences are maximised. We selected the lowest number across the study cohort and used this as an upper value of the proportional threshold procedure, defined as Tmax. The structural connectivity networks were thresholded from a density of 0.5% to Tmax with the *threshold_proportional* command in the Brain Connectivity Toolbox (Rubinov and Sporns, 2010), and the same surviving edges were kept for the $FA_{mean}$ networks. At each cost-thresholded level, nodal strength for every brain region was calculated using the Brain Connectivity Toolbox for Matlab (Rubinov and Sporns, 2010).

### 2.8. Statistical methods

#### 2.8.1. Demographic, neurodevelopmental, and cognitive data

Descriptive statistics comprised mean and standard deviation for the continuous variables and numbers and percentages of total for the categorical variables. The comparison of demographic and neurodevelopmental data between study groups was conducted using independent samples *t*-test, Wilcoxon rank-sum test, or Chi-squared test, as appropriate. Using linear regression, the effect of preterm birth on inhibition abilities was quantified. The regression analyses were adjusted for age at assessment, sex, and SES to account for potential confounding bias. In order to avoid the exclusion of study cases from the model due to missing information on (one of) the parents' education ($n$ = 8), single imputation was applied for missing SES data. As the EpoKids study is currently ongoing, continued blinding of the study team needs to be ensured. Thus, the assignment at birth to either the intervention or placebo arm was encoded as 'intervention 1' vs. 'intervention 2' by the staff of the original trial. Potential intervention effects were addressed by comparing neurodevelopmental outcomes between the treatment groups. No differences were found for IQ estimate, SSRT, and Color Word inhibition time. Therefore, the treatment arm was not further taken into account when performing statistical analysis on the cognitive data, and data of all very preterm participants were pooled. Statistical analyses were performed using *R* statistical software, Version 3.5.3 (R Core Team, 2018; Yoshida et al., 2018; Fletcher, 2012; Lüdecke, 2019; Fox and Weisberg, 2019). *P*-Values $<$ 0.05 were considered statistically significant.

#### 2.8.2. Group differences in FA-weighted global network connectivity and association of FA-weighted global network connectivity with inhibition abilities

First, to avoid introducing systematic connectivity differences between the case and control groups by the proportional cost thresholding, we tested if overall structural connectivity is different between groups

(van den Heuvel et al., 2017). This was calculated by averaging the edge-wise mean FA values in all edges in the unthresholded connectivity matrices. Next, we chose one cost threshold value for thresholding the connectivity matrices that was empirically proven to be most sensitive for preterm-control differences. This was determined as the cost threshold value where the number of nodes significantly different between preterm and control groups was maximal. During this mass-multivariate testing of nodal values across brain regions, statistical significance was adjusted for multiple comparisons using the Benjamini-Hochberg procedure, implemented in the FDR toolbox in Matlab R2014 (Mathworks, 2014). Additionally, we repeated our experiments on unthresholded connectivity matrices as well as the overall structural connectivity strength included as a covariate in the models.

Next, the inference of interest was whether the linear relationship between inhibition abilities and global $FA_{mean}$ differs between participants born very preterm and participants born at term. Hypothesis tests on structural connectivity networks were based on the network-based statistics (NBS) method described by Zalesky et al. (2010), which was implemented in the NBS Toolbox for Matlab R2014. NBS avoids the problem of multiple comparisons during mass univariate tests on connectivity networks by estimating statistical significance for subsets of mutually connected network nodes in topological rather than physical space (Reess et al., 2016). The NBS method comprises four steps. First, the *t*-statistic for each individual edge in the connectivity network is calculated. Second, a primary component-forming threshold ($p < 0.05$, uncorrected) is applied to identify edges displaying differences in connectivity strength. Third, subthreshold edges are assessed for mutual connections forming clusters in topological space that may point toward the existence of non-chance clusters. Fourth, a test with 5000 random permutations is applied to compute statistical significance for all previously identified network components. As NBS uses permutation test to build up the sample distribution, it can be applied to smaller study groups without assuming normality. The final hypothesis test is then carried out for the empirically determined components by comparing their extent with the proportion of permutations yielding a component with equal or greater size, correcting for the family-wise error rate at cluster level with $p < 0.05$. In our tests, a primary threshold *t*-score of 2.5 was chosen.

In all statistical evaluations, SES, sex, and age at assessment were included into the model as parameters that may have an effect on the structural connectivity values averaged over the networks from the NBS analysis. The design and contrast matrices used during NBS for group differences and simple correlations are given in Table S1. We further tested whether preterm and control grouping variable ("birth status") has an effect on the correlation between inhibition abilities and structural connectivity by performing a statistical test with continuous covariate interaction (contrast and design matrix: Table S2). As Epo treatment was previously reported to have an effect on structural brain connectivity in preterms at term equivalent age (Jakab et al., 2019), all statistical tests were repeated with both the Epo treatment and preterm status as covariates in the model (contrast and design matrix: Table S3). In case of no effect was seen for the Epo treatment on the connectivity topology, we removed this variable in order to avoid overfitting the regression model by having too many parameters. A similar consideration was made for including global structural connectivity as covariate in the model (contrast and design matrix: Table S4).

We presented the results of the NBS as three-dimensional graph visualizations, which represented below *p*-threshold connection pairs surviving multiple comparison correction. The brain networks were visualized with the BrainNet Viewer for Matlab R2014 (Xia et al., 2013).

## 3. Data availability

All raw data and scripts used for the calculations and figure generation in this manuscript can be obtained by contacting the corresponding author.

## 4. Results

### 4.1. Sample characteristics

Of 180 eligible participants, 100 children and their parents agreed to take part in the EpoKids study (55.6%). Children who took part in the EpoKids study did not differ from those who did not with regard to gestational age, birth weight, neonatal complications (BPD, NEC, ROP, major brain lesions), and Bayley scores (Bayley, 1993) at 2 years of age (all $p > 0.05$). SES of the parents was higher in participants than in non-participants ($p = 0.004$). Fourteen families agreed to complete questionnaires only and seven participants living in Western Switzerland were assessed by study collaborators in Geneva, Switzerland, who were trained for this purpose. These participants did not undergo an MRI assessment. Thus, for these 21 participants, the measures relevant for the current analyses were not available and they were not further considered. Of the remaining participants (79 born very preterm, 78 born at term), 12 participants born very preterm and 10 participants born at term were not administered one or both of the inhibition tasks due to technical issues or indication of fatigue and were excluded from the current analyses. The final sample, thus, included 67 very preterm and 69 term-born participants. To test for a potential selection bias, participants with and without complete inhibition data were compared with regard to sex, age at assessment, SES, and estimated IQ. These analyses did not reveal any differences (all $p > 0.05$).

Table 1 summarizes demographic, socioeconomic, cognitive, and perinatal data of all participants. No group differences were found for sex and age at assessment. SES was higher in families of term-born participants. The very preterm born group had a lower estimated IQ than the term-born group.

### 4.2. Inhibition abilities in the very preterm and the term-born group

Using independent samples *t*-tests, the overall inhibition composite score was lower in the very preterm group than in the term-born group. When regarding the two inhibition measures separately, only the *z*-score of the SSRT was lower in the very preterm than in the term-born group. When adjusting for age at assessment, sex and SES, differences in the overall inhibition composite score were not significantly explained by preterm birth ($\beta = -0.13$, 95%-CI [-0.30, 0.04], $p = 0.13$; adjusted $R^2 = 0.19$, $p < 0.001$). Differences in the SSRT were significantly explained by preterm birth when adjusting for age at assessment, sex, and SES ($\beta = -0.25$, 95%-CI [-0.43, −0.08], $p = 0.006$; adjusted $R^2 = 0.11$, $p < 0.001$). Differences in Color Word inhibition time were not explained by preterm birth when adjusting for age at assessment, sex, and SES ($\beta = 0.07$, 95%-CI [-0.11, 0.24], $p = 0.46$; adjusted $R^2 = 0.15$, $p < 0.001$).

### 4.3. Availability and quality of DTI data

Nine children born very preterm and four children born at term refused (full) MRI assessment, thus, no DTI data were available. Additionally, the DTI data of eight children born very preterm and four children born at term had to be excluded from analyses due to poor data quality (i.e., strong movement artifacts, susceptibility artifacts caused by orthodontic appliances). This results in a subsample of 50 children born very preterm and 62 children born at term with DTI data. Participants with and without DTI data were compared with regard to birth status, sex, age at assessment, SES, and estimated IQ: this analyses revealed lower age at assessment for children without DTI data ($p = 0.035$). Further, for more children born very preterm ($n = 17$) than children born at term ($n = 7$) DTI data were not available ($p = 0.035$). Sex distribution, SES, and estimated IQ were comparable between groups (all $p > 0.05$).

**Table 1**
Sample characteristics.

| | very preterm-born $n = 67$ | | | term-born $n = 69$ | | | $p$[a] |
|---|---|---|---|---|---|---|---|
| Demographic and socioeconomic data | | | | | | | |
| Female, *n* (%) | 28 (41.8) | | | 32 (46.4) | | | .72 |
| | *M* | *SD* | *range* | *M* | *SD* | *range* | |
| Age at assessment (in years) | 10.8 | 1.2 | [8.8–13.4] | 11.1 | 1.3 | [8.8–13.5] | .18 |
| Socioeconomic status[b] | 7.9 | 2.0 | [4–12] | 9.7 | 2.1 | [6–12] | <.001 |
| Perinatal data | | | | | | | |
| Gestational age (in weeks) | 29.3 | 1.7 | [26.0–31.7] | 39.6 | 1.1 | [37.3–42.0] | |
| Birthweight (in grams) | 1210 | 317 | [570–2020] | 3470 | 448 | [2370–4410] | |
| Moderate or severe BPD, *n* (%) | 7 (10.4) | | | – | | | |
| ROP ≥ grade 3, *n* (%) | 0 (0) | | | – | | | |
| NEC, *n* (%) | 3 (4.5) | | | – | | | |
| Major brain lesions, *n* (%) | 2 (3) | | | – | | | |
| Cognitive data | *M* | *SD* | *range* | *M* | *SD* | *range* | |
| IQ estimate | 102 | 16.5 | [67.1–138] | 115 | 13.7 | [83.7–152] | <.001 |
| Inhibition composite score[c] | −0.4 | 0.8 | [-2.2-1.7] | 0.0 | 0.8 | [-2.3-1.5] | .007 |
| Stop signal reaction time (SSRT)[c] | −0.6 | 1.1 | [-3.5-3.1] | 0.0 | 1.0 | [-2.9-1.9] | .001 |
| Color Word inhibition time[c] | −0.1 | 0.9 | [-2.8-1.5] | 0.0 | 1.0 | [-3.1-1.5] | 0.5 |

*M*: mean; *SD*: standard deviation; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis.
[a] Independent samples *t*-tests.
[b] Possible range for total SES scores: 2–12. Missing SES data: $n = 8$.
[c] *Z*-scores calculated with *M* und *SD* of term-born group.

### 4.4. Group comparison of FA-weighted whole-brain structural connectivity on network level

The overall structural connectivity strength of controls was significantly higher than of very preterm children ($t = 2.634$, $p = 0.0095$). To evaluate regional differences in network topology between very preterm children and controls, connectivity networks were analysed after the proportional thresholding. We evaluated which network sparsity threshold is most sensitive for the differences between children born very preterm and at term. The minimum cost of structural connectivity networks in the overall study population was 0.28, therefore this was used as upper threshold for iterative cost thresholding. At each cost threshold, multivariate analysis of variance was performed for each brain region, testing the group differences in nodal connectivity strength, using a model adjusted for the effect of age at assessment, sex and SES. The maximum number of nodes (8) affected by premature birth (FDR-corrected $p < 0.05$) was found at cost = 0.21. Intermediate steps of the iterative cost thresholding procedure are illustrated in Fig. 1A. We tested network-level differences at various cost thresholds: this analysis showed a largely similar network. In sparse connectivity matrices, the network was predominantly limited to bilateral frontal, left parietal, temporal and subcortical connections, while with increasing density, more inter- and intra-hemispheric connections were different between the two study groups. NBS revealed a network comprising thalamo-frontal, thalamo-temporal, bilateral frontal, cerebellar and various intra-hemispheric connections that had significantly lower structural connectivity in the preterm children ($t = 5.21$, lowest $p$-value = 0.001) in a model adjusted for age at assessment, sex and SES (design matrix is shown in Table S5, resulting network: Fig. 2A). This network consisted of 117 edges (7.8% of the total network edges at cost = 0.21). The average FA value was 4.45% lower in children born very preterm than in children born at term (FA = 0.45 ± 0.017 and 0.47 ± 0.023, respectively; Fig. 2B). The regions with the highest number of connections affected by preterm birth were the left middle temporal gyrus, the left and right thalamus, the left inferior temporal gyrus, the left cerebellum, the right anterior cingulate gyrus, the left and right orbital part of inferior frontal gyrus, and the medial part of the right superior frontal gyrus.

The overall network topology remained similar when testing unthresholded connectivity networks with considerably more weak connections being different (Fig. 1). The inclusion of overall structural connectivity and Epo treatment arm as covariates in the model did not change the topology considerably (Fig. S2).

### 4.5. Association of FA-weighted whole-brain structural connectivity and inhibition abilities

Across both study groups, NBS revealed an extensive network consisting of 54 edges in which overall inhibition abilities were positively associated with FA-weighted structural connectivity ($t = 4.23$, lowest $p$-value = 0.02) in a model adjusted for age at assessment, sex and SES. This network comprised predominantly parietal, cerebellar and subcortical connections (design matrix is shown in Table S3, resulting network: Fig. 3A). The regions with the highest number of connections significantly correlated with overall inhibition abilities were the left and right cerebellum, the left thalamus, the right inferior parietal lobule, the right superior parietal lobule, and the right Heschl's gyrus. Whereas the graphical illustration of the continuous covariate interaction suggests divergent associations of the significant network relevant for overall inhibition in the two study groups (see Fig. 3B), the interaction did not reach statistical significance ($t = 3.75$, lowest $p$-value = 0.09; design matrix is shown in Table S3). Interestingly, overall FA was moderately correlated with the overall inhibition abilities ($r = .279$, $p = 0.0028$), even after controlling for the birth status, which rules out the possible confounding effect of preterm birth on the connectivity network. Therefore, including the overall FA as a covariate in the model diminished the regional effects revealed previously and NBS did not find any network where overall inhibition score and structural connectivity were correlated. The inclusion of Epo treatment arm as covariates in the model did not change the topology of edges correlated with overall inhibition abilities and a largely similar network was revealed when performing the analysis on unthresholded connectivity networks (Fig. S3).

When looking separately at associations of structural connectivity with the two distinct components of inhibition abilities, $FA_{mean}$ correlated significantly with the domain *interference control*, measured by Color Word inhibition time ($t = 4.36$, lowest $p$-value = 0.002; see Fig. 4A and B) in a network comprising 58 edges in both study groups. The regions with the highest number of connections significantly correlated with *interference control* were the left putamen, the left thalamus, the right superior parietal lobule, the right superior occipital gyrus, the left anterior cingulate gyrus, the right middle cingulate gyrus, the right middle

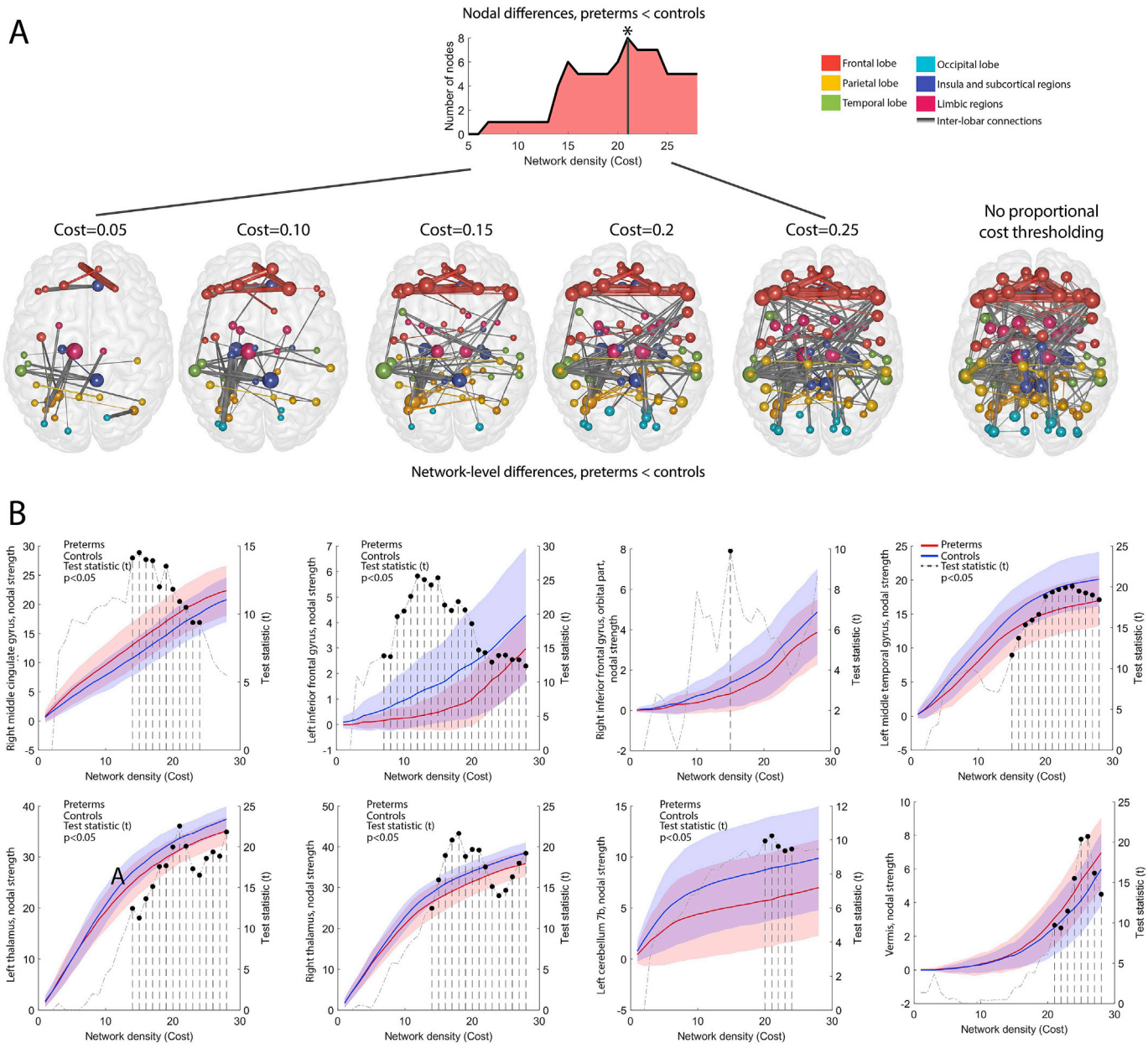


**Fig. 1. A. Network-level differences in the structural brain connectivity of preterm and control children.** Intermediate steps of the iterative thresholding procedure based on network density (cost). Right image: results using unthresholded structural connectivity network.
**B. Nodal differences in the structural brain connectivity of preterm and control children.** The maximum number of nodes (8) affected by very preterm birth (FDR-corrected $p < 0.05$) was found at cost = 0.21.

frontal gyrus, the left inferior parietal lobule, the left cerebellum, and the left Heschl's gyrus. $FA_{mean}$ did not correlate with *response inhibition*, measured by SSRT ($t = 4.19$, lowest $p$-value = 0.91). Overall FA was only weakly correlated with the domain *interference control* (r = .212, $p$ = 0.0244), and including the overall FA in the statistical model resulted in a largely similar network as without this variable (comparison: Fig. S4).

## 5. Discussion

The current study investigated differences in inhibition abilities between children born very preterm and term-born peers at middle school-age and compared whole-brain structural connectivity on network level between these two groups. To the best of our knowledge, this is the first study to investigate the association between inhibition abilities and whole-brain structural connectivity on network level in children born very preterm and children born at term. In our study, overall inhibition abilities were comparable between middle school-aged children born very preterm and their term-born peers, although group differences were observed for the subtest of response inhibition. Global structural brain connectivity measured as mean fractional anisotropy differed significantly between children born very preterm and term-born peers, particularly in frontal and temporal regions, the cerebellum and the thalamus. Irrespective of birth status, overall structural connectivity as well as regional connectivity in parietal and temporal brain regions, the cerebellum and the thalamus was significantly associated with overall inhibition abilities and the subtest of interference control.

The term *inhibition abilities* describes two inter-related but distinct components of inhibitory control: response inhibition and interference control. Response inhibition describes the ability to deliberately suppress, interrupt or delay an action (Clark, 1996; Friedman and Miyake,

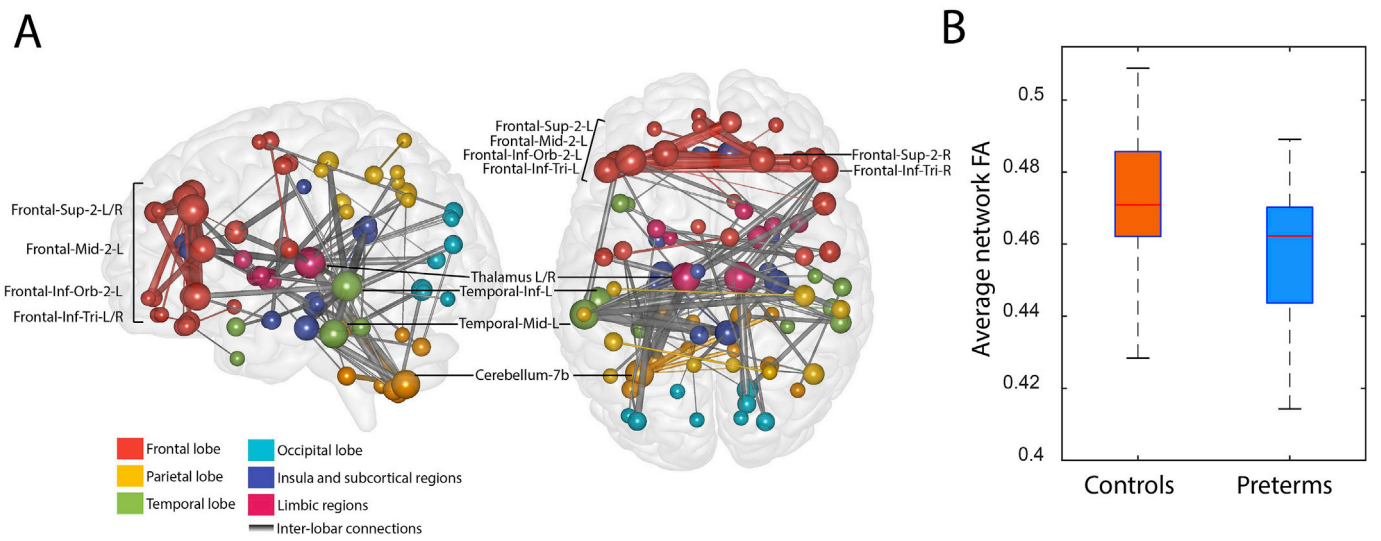


**Fig. 2. A.** (Sagittal and axial view of) NBS revealed-network with significantly lower $FA_{mean}$ in the preterm children ($t = 5.21$, lowest $p$-value $= 0.001$) in a model adjusted for age, sex and SES. The network comprises thalamo-frontal, thalamo-temporal, bilateral frontal, cerebellar, and various intra-hemispheric connections. **B.** Average FA value in NBS revealed-network with significantly lower $FA_{mean}$ in preterm children. The average FA value was 4.45% lower in the preterm children than in children born at term (FA $= 0.45 \pm 0.017$ and $0.47 \pm 0.023$, respectively).

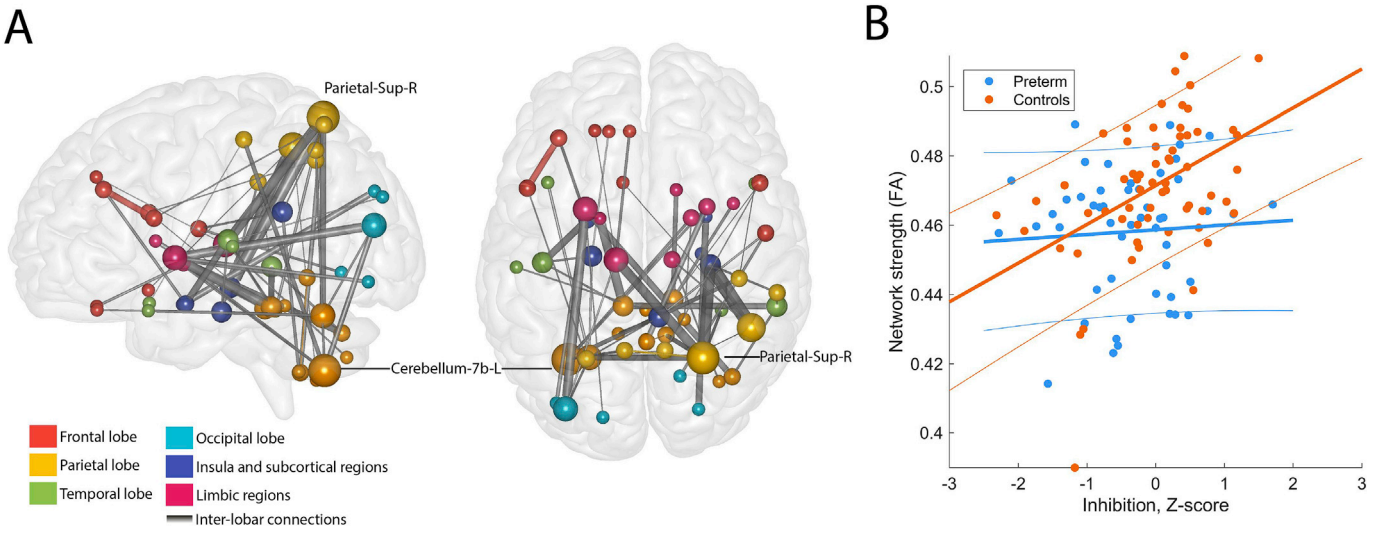


**Fig. 3. A.** (Sagittal and axial view of) NBS revealed-network in which, irrespective of birth status, overall inhibition abilities were positively associated with $FA_{mean}$ ($t = 4.23$, lowest $p$-value $= 0.02$) in a model adjusted for age, sex and SES. The network comprises predominantly parietal, cerebellar, and subcortical connections. **B.** Graphical illustration of the association of FA values with inhibition composite score for study groups, separately. The interaction did not reach statistical significance ($t = 3.75$, lowest $p$-value $= 0.09$).

2004; Nigg, 2000), interference control describes the ability to selectively attend to relevant information while filtering out distracting or competing information (Friedman and Miyake, 2004; Nigg, 2000). The stop-signal task (Verbruggen and Logan, 2008) is commonly used to measure response inhibition, whereas interference control is often assessed by Stroop tasks, such as the D-KEFS' Color-Word Interference Test (Delis et al., 2001) (see Réveillon et al. (2018) for an overview of instruments to assess inhibition abilities). In our study, a statistically relevant effect of very preterm birth on response inhibition but not on interference control was observed when controlling for sex, SES and age at assessment. Interestingly, response inhibition has also been shown to be one of the primarily impaired functions in patients with attention disorders like ADHD (Wodka et al., 2007), a condition two to four times more prevalent in the preterm than in the general population (Arpino et al., 2010; Bhutta et al., 2002; Johnson and Wolke, 2013). The divergent finding of impaired response inhibition and intact interference control is largely in line with existing literature (Aarnoudse-Moens et al., 2012; Bayless and Stevenson, 2007; Elgen et al., 2004; Anderson et al., 2011; Ritter et al., 2014; Shum et al., 2008; Baron et al., 2014). Some studies have, however, also reported group differences in interference control (Loe et al., 2012; de Kieviet et al., 2014; Ritter et al., 2013a; Ford et al., 2011; Elgen et al., 2004; Johnson et al., 2015; Mulder et al., 2011b). To some extent, these ambiguous findings may be explained by differences in perinatal characteristics, age at assessment, or assessment instruments. For example, Ford et al., 2011 and Mulder et al., 2011b reported group differences on both inhibition domains in a cohort of very preterm children born at a younger mean gestational age compared to the preterm cohort assessed in this study. It has been shown that the risk of executive function deficits increases with decreasing gestational age (Anderson and Doyle, 2004; Aarnoudse-Moens et al., 2009b), with inhibition abilities being particularly affected (Ritter et al., 2013b). This effect could explain why in our preterm cohort not all aspects of

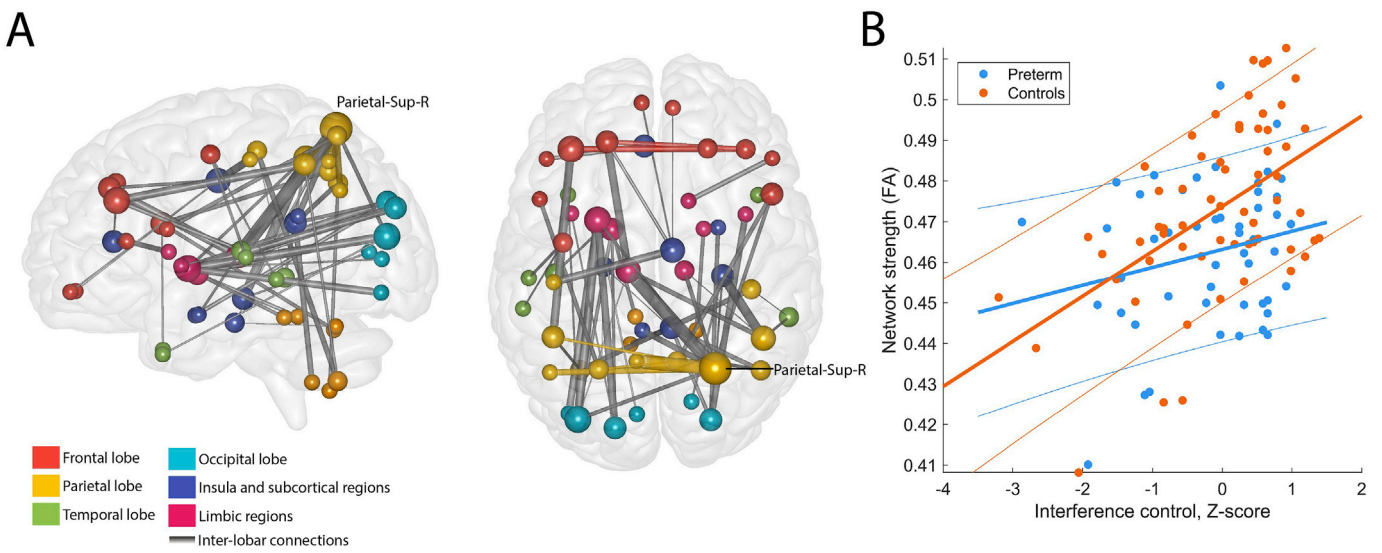


**Fig. 4. A.** (Sagittal and axial view of) NBS revealed-network in which, irrespective of birth status, Color Word inhibition time (*interference control*) was positively associated with $FA_{mean}$ ($t = 4.36$, lowest $p$-value $= 0.002$) in a model adjusted for age, sex and SES. The network comprises predominantly frontal, parietal, occipital, and subcortical connections. **B.** Graphical illustration of the association of FA values with Color Word inhibition time (*interference control*) for study groups, separately. The interaction did not reach statistical significance.

inhibitory abilities were impaired. Other studies reported interference control deficits in younger very preterm children (de Kieviet et al., 2014; Ritter et al., 2013a; Ford et al., 2011; Mulder et al., 2011b), thereby potentially addressing a more at-risk-population since inhibition abilities develop throughout childhood and adolescence (Huizinga et al., 2006). Lastly, differences in quantifying inhibition abilities might lead to incongruent study results: In fact, studies reporting deficits in interference control (vs. unimpaired interference abilities in this study) (Loe et al., 2012; Ford et al., 2011) or unimpaired response inhibition (vs. deficits in this study) (Loe et al., 2012; Elgen et al., 2004; Johnson et al., 2015) have used error rate/accuracy as outcome measures of inhibition tasks while the current study assessed reaction time. Taken together, our results add to a vivid discourse on inhibition abilities in children born very preterm: do the reported impairments represent actual deficits or do inhibition abilities in children born very preterm develop in a delayed manner (Aarnoudse-Moens et al., 2012; Ritter et al., 2013a; Réveillon et al., 2018)? Inhibition abilities are known to develop between the ages of 4–12 years (Best and Miller, 2010), with some studies suggesting stabilization between 9 and 12 years (Tillman et al., 2007; Urben et al., 2011; Williams et al., 1999). Given the age range of our preterm participants, it is possible that they have already grown out of a possible risk to show impaired inhibition abilities. Moreover, age at assessment proved to be the strongest predictor for all domains of inhibition abilities in the current study. This highlights the importance to consider age when investigating inhibition abilities in childhood. Eventually, only longitudinal data can contribute in a meaningful and satisfying manner to this ongoing discourse (Baron et al., 2014; Everts et al., 2019).

We found significant differences in global structural brain connectivity between children born very preterm and term-born peers, with predilection in frontal and temporal regions, the cerebellum and the thalamus. These topological differences remained when performing the same test on unthresholded network as well as when overall connectivity was controlled for, therefore, the very preterm-control differences are likely not caused by the proportional thresholding procedure (van den Heuvel et al., 2017). The present work confirms the long-term adverse effects of very preterm birth on white matter microstructure throughout childhood and adolescence, using a whole-brain approach which allows for conclusions on network-level. Importantly, during the third trimester of pregnancy, significant maturational processes such as the differentiation of pre-oligodendrocytes, the emergence of thalamo-cortical connections, cortical folding, and increase of functional connectivity are known to take place across various brain structures and regions (Jakab et al., 2019; Ortinau and Neil, 2015; Young, 2019). Axonal development generates all major pathways in the preterm period. After birth, through myelination, the established networks further mature until adolescence (Dubois et al., 2015). Early injury resulting from hypoxia/ischemia or infection/inflammation, of which both are common during the preterm period (Ortinau and Neil, 2015), is likely to cause aberrant microstructural development of the cortex, thalamus, and connecting white matter tracts (Ghosh and Shatz, 1993; Pierson et al., 2007; Volpe, 2009a; Dean et al., 2013) in children born very preterm. Against this background, the present analysis classifies all cortical and sub-cortical seed points and end points of relevant connections (Jakab et al., 2019) and thus provides information exceeding subjective, hypothesis-driven approaches, which only take into account a limited number of pre-defined white matter tracts and may thus lead to incomplete results (Hagmann et al., 2007). Alterations in regional structural connectivity have been reported in individuals born very preterm at term age (Batalle et al., 2017; Thompson et al., 2011, 2014; Hüppi et al., 1996; Mewes et al., 2006; Ball et al., 2013; Anjari et al., 2007), throughout early childhood (Pandit et al., 2013; Counsell et al., 2008), in adolescence (Mullen et al., 2011; Vangberg et al., 2006), and early adulthood (Eikenes et al., 2011; Nosarti et al., 2014) (for a review on aberrant structural – and functional – brain connectivity in children born preterm, see Rogers et al. (2018)). However, only a small number of studies have examined structural connectivity of prematurely born children at network-level (Batalle et al., 2017; Pandit et al., 2013; Ball et al., 2014; Tymofiyeva et al., 2012; Kim et al., 2014; Fischi-Gómez et al., 2014). In infancy, reduced connectivity in the thalamus, the cerebellum, the frontal lobe and the cingulate gyrus have been described (Batalle et al., 2017; Pandit et al., 2013; Ball et al., 2014; Tymofiyeva et al., 2012). At early school age (mean ages 6 years and 8 years, respectively), lower gestational age was related to decreased efficiency in a widespread network comprising the frontal, parietal, temporal, medial, and orbital cortex, the precuneus, cuneus, and subcortical gray matter (Fischi-Gómez, 2014; Kim, 2014). The present study confirms these findings for older preterm born children at middle school-age: The effect of very preterm birth on the whole-brain topology of structural brain networks is still apparent in an extended bilateral network including the frontal, parietal and temporal lobes and several subcortical structures. Resulting from a non-hypothesis driven analysis of DTI data,

the strongest group differences were found for white matter connections serving the left and right orbital part of the inferior frontal gyrus, the left middle temporal gyrus, the right middle cingulate gyrus, the right anterior cingulate gyrus, the medial part of the right superior frontal gyrus, the left and right thalamus, and the left cerebellum. These results are in line with previous studies using regional approaches that have reported reduced FA associated with very preterm birth in the aforementioned connections (Volpe, 2009a, 2009b; Thompson et al., 2014; Ball et al., 2013; Mullen et al., 2011; Eikenes et al., 2011; Meng et al., 2016; Hart et al., 2010; Cui et al., 2017). However, none of these studies have shown such widespread differences.

Interestingly, in the present study, structural networks correlating with inhibition abilities do not overlap with the networks that differ between children born very preterm and term-born peers. Thus, it seems that altered structural connectivity may not directly underlie group differences in inhibition abilities. Still, this study presents evidence that, regardless of birth status (i.e., born very preterm vs. born at term), overall inhibition abilities in a cohort of middle school-aged children are associated with measures of structural connectivity at network-level. Brain networks that we found to be associated with inhibition performance of participants across both groups involved the left and right cerebellum, the left thalamus, the right inferior parietal lobule, the right superior parietal lobule, the right superior occipital lobule, and the right Heschl's gyrus. Previous studies investigating the association between regional white matter structure and inhibition have almost exclusively focused on typically-developing children and adults. These studies found that better inhibition performance was associated with higher FA in the corpus callosum, the anterior corona radiata, and in connections serving the inferior frontal gyrus, the pre-supplementary motor area and the subthalamic nucleus (Madsen et al., 2010; Seghete et al., 2013; Chaddock-Heyman et al., 2013; Forstmann et al., 2008, 2012; King et al., 2012; Treit et al., 2014). Surprisingly, in the present analyses, associations of $FA_{mean}$ in tracts serving the aforementioned brain areas and inhibition performance were not found. This might be due to differences in age at assessment, measurements of inhibition abilities, or approaches to DTI analysis. To date, only one other study has examined the association between inhibition abilities, namely interference control, and structural connectivity in children born very preterm and at term: de Kieviet et al. (2014) found decreased FA in children born very preterm compared to term-born peers in tracts connecting the thalamus with the dorsal anterior cingulate cortex, and the left and right parietal cortex was found to be associated with differences in inhibition abilities (de Kieviet et al., 2014). This is partly in line with findings of the current study. However, de Kieviet et al. (2014) used a hypothesis-driven approach by looking at FA only in tracts that beforehand had shown aberrant functional connectivity during an inhibition task for children born very preterm, which is why the comparability of findings is limited.

In contrast to the very limited understanding of the association between inhibition abilities and structural connectivity, considerably more studies report on associations with functional connectivity in individuals born preterm (Nosarti et al., 2006; Griffiths et al., 2013; Lawrence et al., 2009; Daamen et al., 2015). These studies mostly report an involvement of the parietal and occipital cortex, the cerebellum and the thalamus in inhibition tasks. Interestingly, these are regions which were identified in the current study of structural connectivity. Additionally, these studies report (altered) activation patterns in the preterm group during inhibition tasks, in the anterior cingulate and prefrontal cortex, and the temporal gyrus (Nosarti et al., 2006; Griffiths et al., 2013; Lawrence et al., 2009; Daamen et al., 2015). To our knowledge, evidence for associations between inhibition performance and the auditory cortex, namely Heschl's gyrus, has only been reported once in a functional neuroimaging study on intentional inhibition (Kühn et al., 2009). While this association was attributed to the auditory stimuli of the inhibition task, additional studies are needed to further examine and verify our result that Heschl's gyrus plays a role in a non-auditory inhibition task.

Previous meta-analytic evidence of functional neuroimaging studies in typically-developing individuals has shown that neural correlates between the distinct components of inhibition can diverge (Zhang et al., 2017). Still, it is rather surprising that the present analyses revealed significant associations between the structural connectivity and measures of interference control (Color Word inhibition time), but not response inhibition (SSRT). This finding is in contrast to results from one previous study of white matter microstructure and very similar measures of response inhibition in a cohort of typically-developing children of comparable age (Madsen et al., 2010). More studies are needed to further comprehend this inconsistency.

### 5.1. Limitations

The sample of children born very preterm in our study shows a high estimated IQ, comes from a high socioeconomic background, and has had few neonatal complications. This is not fully representative of the general population of children born very preterm (Anderson, 2014). It might also explain why group differences in inhibition performance, while partly statistically significant, are rather small between children born very preterm and at term. Further, excluding several participants due to motion or dental braces artifacts resulted in a less well-balanced cohort eligible for the DTI analysis with regard to birth status and age at assessment. This may have impacted the representativeness of imaging results. A further limitation is the use of adult neuroimaging templates (FMRIB58 FA template in the MNI152 space). This choice was based on the availability of AAL ROIs in this particular template space and also the fact that in our study population, the brain has almost reached its adult size, therefore as far as the overall geometric bias and volumes are concerned, adult templates would be closer to our subject age (8-13 years of age) than the younger imaging templates, such as newborn or 2-year old templates. Structural connectomic analysis is limited by the inaccurate estimation of FA values in regions with complex fiber anatomy, such as in crossing-fiber regions. A simulation study calls for careful attention when interpreting the results of connectomic analysis in case-control studies (van den Heuvel et al., 2017), as systematic differences can emerge simply because of the thresholding procedure used. To overcome this problem, we repeated all our experiments on unthresholded networks as well as using models where overall connectivity is controlled for.

Overall, the comprehensive study protocol of the EpoKids study led to a reduced study cohort when compared to the number of children that were eligible for the present analyses. However, the sample size is still comparable to other studies in this research field (de Kieviet et al., 2014; Madsen et al., 2010; Seghete et al., 2013; King et al., 2012).

## 6. Conclusion

The present analyses show long-term effects of preterm birth on white matter development at network-level alongside comparable overall inhibition abilities in very preterm children at middle school-age compared to term-born peers. As the structural networks underlying inhibition abilities are the same in both study groups, the investigation of network-level structural connectivity in terms of $FA_{mean}$ does not appear adequate to explain differences in inhibition abilities between children born very preterm and at term. Likely, considering and combining complementary parameters of structural connectivity, such as properties investigated with a graph theoretic approach (e.g., local and global efficiency, clustering coefficient, betweenness centrality), and functional brain activation patterns will shed light on these issues in the future.

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and the Hermann Klaus Stiftung.

## Declaration of competing interest

The authors declare that they have no competing interests.

## CRediT authorship contribution statement

**Vera Disselhoff:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Visualization, Writing - original draft. **Andras Jakab:** Methodology, Formal analysis, Software, Validation, Writing - original draft, Visualization. **Barbara Schnider:** Investigation, Resources, Data curation, Writing - review & editing. **Beatrice Latal:** Conceptualization, Resources, Writing - review & editing. **Flavia M. Wehrle:** Conceptualization, Methodology, Validation, Data curation, Resources, Writing - review & editing, Supervision, Project administration. **Cornelia F. Hagmann:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Resources, Project administration, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116937.

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